Testosterone

Brand Name: Androgel, Testoderm, Androderm, Depo-Testosterone

Drug Description

Testosterone is a naturally occurring androgenic steroid hormone. The drug may be obtained from animal testes but is usually prepared synthetically from cholesterol. [1]

HIV/AIDS-Related Uses

Testosterone (transdermal and injection) is used to treat AIDS wasting syndrome in HIV infected men.[2] It is being investigated to assess its efficacy in reducing symptoms of increased visceral fat in HIV infected men.[3] Transdermal testosterone is also being investigated to determine its safety and efficacy in treating weight loss in HIV infected women.[4]

Non-HIV/AIDS-Related Uses

Testosterone (transdermal and injection) is approved by the FDA for hormone replacement therapy in males with a congenital or acquired deficiency or absence of endogenous testosterone. Injection testosterone is also approved for the treatment of metastatic breast cancer in women.[5]

Pharmacology

Testosterone is the principal endogenous androgen. Endogenous androgens are responsible for a number of physical conditions, including alterations in body musculature and fat distribution. Loss of lean body mass is a common complication of HIV/AIDS, and HIV infected individuals undergoing highly active antiretroviral therapy (HAART) have a high incidence of lipodystrophy. While the pathophysiologies of wasting and visceral obesity common to HIV infection are multifactorial, testosterone replacement appears to have a favorable impact on these syndromes.[6]

Testosterone produces retention of nitrogen, potassium, sodium, and phosphorus and increases protein anabolism.[7] Androgens are highly lipid-soluble and enter target cells by passive diffusion. Testosterone or the metabolite 5-alpha-dihydrotesosterone binds to an intracellular androgen receptor, which then translocates to the nucleus and attaches to specific hormone receptor elements on the chromosome. This process initiates or suppresses transcription and protein synthesis.[8]

Androgens also stimulate red blood cell production by enhancing production of erythropoietic stimulating factors.[9]

Esters of testosterone cypionate and testosterone enanthate given via intramuscular (IM) injection are absorbed slowly from the lipid tissue phase at the injection site, with peak serum concentrations reached about 72 hours after the dose is given. These esters' slow absorption results in a prolonged duration of action of 2 to 4 weeks after administration. By contrast, testosterone propionate given by IM injection has a comparatively short duration of action. Irritation at the IM injection site may cause erratic absorption of any testosterone ester.[10]

Transdermal testosterone is absorbed systemically through the skin. Approximately 10% of a testosterone gel dose is absorbed into systemic circulation. Increases in serum testosterone concentrations occur within 30 minutes of the application of a 100-mg dose of 1% gel. In most patients, physiologic concentrations are achieved within 4 hours, with percutaneous absorption maintained throughout the 24-hour dosing period. Serum testosterone concentrations reach steady state by the second or third day of dosing with the 1% gel.[11]

Percutaneous absorption of testosterone via transdermal systems varies considerably among individual patients; however, serum testosterone concentrations generally reach the normal physiologic range within the first day of dosing. These levels are maintained with no accumulation of testosterone during continuous dosing. Because genital skin contains high concentrations of 5 alpha-reductase, serum concentrations of the active metabolite dihydrotestosterone (DHT) are generally in the supraphysiologic range for men following chronic scrotal application of testosterone transdermal systems. In some men, however, DHT concentrations may increase initially and then decrease to normal levels with continued

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Pharmacology (cont.)

therapy.[12]

Testosterone is in FDA Pregnancy Category X. Studies in humans have shown that androgens cause masculinization of the external genitalia of the female fetus.[13] Because the risks clearly outweigh the possible benefits in women who are pregnant or who can become pregnant, androgens are contraindicated in these patients.[14] It is not known whether testosterone is distributed into breast milk; however, because of the potential for adverse effects in the nursing infant, androgens are not recommended for women who are breast-feeding.[15]

Approximately 40% of circulating plasma testosterone binds to sex hormone-binding globulin (SHBG), 2% remains unbound (free), and the remainder binds to albumin and other proteins. The fraction bound to albumin dissociates easily and is presumed to be biologically active, whereas the SHBG fraction is not.[16]

The plasma half-life of testosterone is highly variable, ranging from 10 to 100 minutes. Testosterone is metabolized principally in the liver to various 17-ketosteroid metabolites, the most active of which are estradiol and DHT. Both testosterone and its metabolites are excreted in urine and feces (approximately 90% and 6%, respectively, of an IM dose).[17]

Adverse Events/Toxicity

The most frequent adverse effects of testosterone include abdominal or back pain; abnormal ejaculation; acne; anxiety; bladder irritability; cholestatic hepatitis, jaundice, and abnormal liver function tests; diarrhea; dizziness; edema; excessive sexual stimulation; flushing of the skin; gynecomastia; habituation; headache; hirsutism; hypercalcemia; increased serum cholesterol; insomnia; libido changes; male pattern baldness; mental depression or irritability; nausea; oligospermia; pain or irritation at injection site; priapism; prostate disorders; redness, burning, or itching at transdermal application site; retention of water, sodium, chloride, potassium, and inorganic phosphates; and seborrhea.[18] [19] [20] [21]

Frequent adverse effects among women receiving testosterone therapy include amenorrhea or other menstrual irregularities, clitoral enlargement, hirsutism, and hoarseness or deepening of the voice.[22]

Pregnant women should not receive testosterone therapy because of the potential for serious harm to the fetus. In addition, pregnant women should avoid skin contact with application sites on patients because of the possibility that transdermal testosterone can be transferred from patients to their sexual partners or others in close physical contact. Potential adverse effects to female offspring exposed to testosterone in utero include clitoral hypertrophy, labial fusion of the external genital fold, abnormal vaginal development, and persistence of a urogenital sinus.[23]

Drug and Food Interactions

Because concurrent administration of testosterone with oral anticoagulants can cause bleeding in some patients, dosage adjustment of anticoagulants may be needed during and after coadministration of the two drugs.[24] Concurrent administration of testosterone with hepatotoxic drugs, including, but not limited to, abacavir, lamivudine, nevirapine, tenofovir, and zidovudine, may increase the incidence of hepatotoxicity.[25] Concurrent administration of testosterone with corticotropin (ACTH) or corticosteroids may enhance edema formation; these drugs should be combined with caution, particularly in patients with cardiac or hepatic disease. Increased clearance of propranolol has been reported in patients receiving the drug concurrently with testosterone cypionate.[26] The use of testosterone by diabetic patients may result in decreased blood glucose levels and reduced insulin requirements. Increased serum levels of oxyphenbutazone have been reported in patients receiving androgens and oxyphenbutazone concurrently.[27]

Contraindications

Testosterone products should not be used in patients with known hypersensitivity to any ingredients in the preparation. Testosterone is contraindicated in men with carcinoma of the breast

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Contraindications (cont.)

or known or suspected carcinoma of the prostate. It is also contraindicated in pregnant or lactating women.[28]

Clinical Trials

For information on clinical trials that involve Testosterone, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Testosterone AND HIV Infections.

Dosing Information

Mode of Delivery: Topical for transdermal absorption; parenteral for intramuscular injection.[29]

Dosage Form: Injectable suspension containing 25, 50, or 100 mg/ml.[30]

Testosterone cypionate or testosterone enanthate injection containing 100 or 200 mg/ml.[31]

Testosterone propionate injection containing 100 mg/ml.[32]

Testosterone gel containing 5, 7.5, or 10 g delivering 50, 75, or 100 mg of testosterone, respectively, per day.[33]

Reservoir-type transdermal system containing 12.2 or 24.3 mg delivering 2.5 or 5 mg of testosterone, respectively, per day.[34]

Matrix-type transdermal system containing 10 or 15 mg delivering 4 or 6 mg of testosterone, respectively, per day.[35]

Storage: Testosterone gel should be stored at controlled room temperature, 20 C to 25 C (68 F to 77 F). Testosterone matrix-type transdermal systems should be stored between 15 C and 30 C (59 F and 86 F).[36]

Chemistry

CAS Name: Androst-4-en-3-one, 17-hydroxy-, (17beta)-[37]

CAS Number: 58-22-0[38]

Molecular formula: C19-H28-O2[39]

C79.12%, H9.78%, O11.09%[40]

Molecular weight: 288.43[41]

Melting point: 155 C[42]

Physical Description: Testosterone is a white to practically white crystalline powder.[43]

Solubility: Practically insoluble in water, freely soluble in dehydrated alcohol, and soluble in vegetable oils.[44]

Other Names

Sustanon[45]

Testosterona[46]

Further Reading

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Manufacturer Information

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Androderm
Watson Laboratories Inc
311 Bonnie Circle
Corona, CA 92880-2882
(800) 272-5525

Depo-Testosterone
Pharmacia Corporation
100 Route 206 North
Peapack, NJ 07977
(888) 768-5501

Depo-Testosterone
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
(800) 438-1985

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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